Table 2: Clinical Study Results of Amerge Tablets in the Treatment of Acute Migraine Attacks in Adolescent Migraineurs (2,3)

Parameter	Placebo	Naratriptan 0.25 mg	Naratriptan 1 mg	Naratriptan 2.5 mg
Patients with headache response at 4 hours*	65%	72%	67%	64%
Patients with no pain at 4 hours	43%	41%	51%	436%
Patients with meaningful relief within 4 hours	65%	76%	71%	66%
Patients without nausea	84%	81%	91%	80%
Patients without photophobia	68%	62%	68%	64%
Patients without phonophobia	73%	73%	73%	71%
Patients with little or no clinical disability**	74%	76%	81%	77%
Patients with recurrence of headache	19%	20%	13%	13%

* Once patients received rescue medication, they were considered treatment failures
** A successful outcome in terms of clinical disability was defined as ability to work mildly impaired or ability to work and function normally

The results indicate that Amerge Tablets and placebo showed comparable efficacy in the acute treatment of migraine as measured by response of headache pain at 4 hours, with no active treatment group showing statistical significance compared to the placebo group. All treatment groups were comparable in treating the secondary endpoints such as associated symptoms, clinical disability, and the use of rescue medication.

Amerge Tablets were well tolerated in this adolescent population. The overall percentages of patients who reported one or more adverse events were higher across all active treatment groups than the placebo group, with no increase in incidence with increasing Amerge Tablets dose: 31% of the 0.25 mg group, 23% of the 1 mg group, 36% of the 2.5 mg group (versus 17% of the placebo group). Nausea/vomiting were the most common individual events in all treatment groups including placebo. Other commonly reported events included migraine and photophobia.

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Enclosure: **Product Information for Amerge™ Tablets, Glaxo Wellcome, Inc.**

RE: USE OF IMITREX® INJECTION, TABLETS, OR NASAL SPRAY IN CHILDREN

SUMMARY

- As noted in the Product Information, the safety and effectiveness of Imitrex® (sumatriptan succinate/sumatriptan), administered either as a subcutaneous (SC) injection, as an oral tablet, or as an intranasal spray has not been established in children (1,2,3). The use of Imitrex in patients less than 18 years of age is not recommended.
- We are aware of several publications regarding the use of Imitrex Injection in children 6-18 years of age are (4,5,6,7) the use of Imitrex Tablets in children 8-18 years of age (8,9,10) and Imitrex Nasal Spray in children 6-18 years of age (11,12).
- A placebo-controlled trial evaluating Imitrex Nasal Spray (5 mg, 10 mg, and 20 mg) in 507 adolescent patients aged 12 to 17 years demonstrated Imitrex Nasal Spray was superior to placebo in relieving migraine pain and associated symptoms and was generally well–tolerated (12,13). Adverse events observed in this clinical trial were similar in nature to those reported in clinical trials in adults. We are also aware of one publication regarding the use of Imitrex Nasal Spray 20 mg in children 6-10 years of age (11).
- The pharmacokinetics of 20 mg of intranasal sumatriptan in adolescent subjects suffering from migraine outside of a migraine attack (mean age, 15; range, 12 to 17 years; 9 females and 12 males) were similar to that in healthy male subjects (mean age, 35.9 years). Since the pharmacokinetics of sumatriptan are linear, these data show that systemic exposure of adolescent subjects after intranasal sumatriptan administration for a given dose is also comparable (14,15,16).
- Placebo-controlled clinical trials evaluating oral sumatriptan (25 to 100 mg) in 701 adolescent patients aged 12 to 17 did not establish the efficacy of oral sumatriptan compared to placebo (2,8,9). Adverse events observed in these clinical trials were similar in nature to those reported in clinical trials in adults. The frequency of all adverse events in these patients appeared to be both dose- and age-dependent, with younger patients reporting events more commonly than older adolescents (2).
- Postmarketing experience includes a limited number of reports that describe pediatric patients who have experienced adverse events, some clinically serious, after use of subcutaneous sumatriptan and/or oral sumatriptan. These reports include events similar in nature to those reported rarely in adults (1,2,3).
- A myocardial infarct has been reported in a 220-pound, 14-year old male, with a reported family history of coronary artery disease (1,2,3,17). Following the use of oral sumatriptan; clinical signs occurred within 1 day of drug administration. On three previous occasions over a period of several months, this patient had received either subcutaneous or oral sumatriptan and had experienced chest pain and/or diaphoresis with malaise after each treatment. The fourth episode of such symptoms, which followed his use of oral sumatriptan, prompted his hospitalization. It was reported that the inpatient evaluation revealed evidence of myocardial injury; an echocardiogram showed hypokinesis and a coronary angiography showed no lesions. Cardiac enzymes were elevated during this admission. The patient was discharged from the hospital three days later.

Some of the information contained in this letter may be outside the product labeling for Imitrex. This letter is not intended to offer an opinion on the advisability of administering Imitrex in a manner inconsistent with the product labeling. Please consult the enclosed product information for complete safety and prescribing information.

BACKGROUND

When reviewing publications regarding the use of any medication for the treatment of migraine in children, it is important to note the following: 1) The International Headache Society (IHS) criteria for migraine in children states that the duration is from 2 to 48 hours versus 4 to 72 hours in adults, and 2) children have a shorter duration of migraines with higher rates of spontaneous resolution after 2 hours (18).

Winner et al (19) have proposed the following revisions to the IHS criteria to facilitate the diagnosis of pediatric migraine: duration–1-48 hours; location–bifrontal/bitemporal or unilateral; and symptoms to include photophobia or phonophobia. These proposed revisions showed significant improvement in diagnostic sensitivity for patients less than 12 years old.

PHARMACOKINETICS

The pharmacokinetics of 20 mg of intranasal sumatriptan in adolescent subjects suffering from migraine outside of a migraine attack was investigated in an open, uncontrolled, study (14). Patients received a single 20 mg dose of intranasal sumatriptan. Plasma samples for determination of sumatriptan concentration were obtained at baseline and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, and 8 hours post-dose. In patients aged 12-17 years, weighing 45 to 78.6 kg, with a height ranging from 140-170 cm, the pharmacokinetics of sumatriptan nasal spray is similar to that observed in adults (15,16). Results are shown in Table 1. Demographic factors such as age, weight, or height did not affect the pharmacokinetics of sumatriptan in adolescents.

Table 1: Comparison of pharmacokinetic variables in Adolescent and Adult Patients

Parameter	Adolescent Patients (14)	Adult Patients (15,16)
C_{max} (ng/mL)	13.89 (10.96, 17.60)	12.9 (10.5, 15.9)
AUC8 (ng/mL*hr)	57.32 (47.61, 69.02)	47.7 (41.1, 55.3)
T½ (hrs)	2.02 (1.77, 2.32)	1.8 (1.7, 2.0)
Median T_{max} (hrs)	2	1.5

Population modeling analysis in adolescents revealed a profile to that observed in adults treated during an attack, with a early absorption phase resulting in a first peak within 30 minutes and a later T_{max} around 2 hours (14,20,21).

IMITREX NASAL SPRAY

Study 1

Winner et al (12,13) presented the results of a randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy of sumatriptan nasal spray in adolescents with migraine.

Methods

IHS-diagnosed migraine patients 12 to 17 years of age were randomized to receive either sumatriptan nasal spray (5mg, 10mg, 20mg) or placebo for the outpatient treatment of one moderate or severe migraine attack. Beginning 2 hours post-dose, patients could take a second blinded dose of study medication for headache recurrence or rescue medication for persistent headache.

The primary efficacy endpoint was the percentage of patients with headache relief (moderate or severe pre-dose pain reduced to mild or no pain) 2 hours post-dose. The percentages of patients with associated

symptoms (nausea, vomiting, photophobia, phonophobia) 2 hours post-dose, using rescue medication 2 to 24 hours post-dose, reporting headache recurrence (return of moderate or severe pain 2 to 24 hours after dosing with study medication in patients reporting headache relief 2 hours post-dose), and reporting any adverse event and specific adverse events were also evaluated.

Results

Six hundred and fifty-three patients were randomized to treatment, and 510 of them treated one attack (507 with evaluable efficacy data). Demographic and baseline migraine characteristics did not differ between groups. Ninety-one percent (91%) of the 510 patients treating a migraine were Caucasian; 51% were female. The mean and median patient age was 14 years.

Results are outlined in Tables 2 and 3. The earliest post-dose time point at which sumatriptan was significantly more effective than placebo in conferring headache relief was 1 hour (10 mg and 20 mg doses only). In a Kaplan-Meier analysis of the estimated probability of headache relief within 2 hours of dosing, each dose of sumatriptan (5 mg, 10 mg, 20 mg) was superior to placebo with respect to the cumulative percentages of patients first reporting pain relief within 2 hours of dosing ($p<0.05$). Photophobia and phonophobia 2 hours post-dose were reported significantly less frequently among patients using sumatriptan nasal spray 20 mg vs. placebo ($p<0.05$). There was no difference between groups in incidence of headache recurrence or use of rescue medication.

The overall incidence of adverse events increased slightly with dose of sumatriptan. Taste disturbance (reported by 2%, 19%, 30%, and 26% of patients in the placebo and sumatriptan 5 mg, 10 mg, and 20 mg groups, respectively) was the most common adverse event. When taste disturbance was not included in the calculation, the overall incidences of adverse events in the sumatriptan groups were similar to or lower than that with placebo. No clinically relevant changes in clinical laboratory parameters, electrocardiograms (ECGs), or vital signs were noted.

Table 2: Efficacy and Tolerability of Imitrex Nasal Spray in Adolescent Migraineurs (12,13)

Parameters	Placebo (n=130)	Imitrex 5 mg (n=127)	Imitrex 10 mg (n=133)	Imitrex 20 mg (n=117)
Headache relief at 1 hour	41%	47%	56%*	56%*
Headache relief at 2 hours	53%	66%*	64%	63%
Pain-free at 2 hours	25%	24%	33%	36%*
Headache Recurrence	20%	18%	20%	16%
Rescue Medication	39%	29%	30%	32%
Any Adverse Event	40%	43%	49%	55%
Any event minus taste disturbance	39%	29%	28%	42%

*p<0.05 vs. placebo

Table 3: Efficacy Of Imitrex Nasal Spray For The Treatment Of Associated Symptoms In Adolescent Migraineurs (12,13)

Associated Symptoms	Placebo (n=130)		Imitrex 5 mg (n=127)		Imitrex 10 mg (n=133)		Imitrex 20 mg (n=117)	
	Predose	2 hours	Predose	2 hours	Predose	2 hours	Predose	2 hours
Nausea	39%	25%	46%	20%	49%	17%	51%	21%
Vomiting	5%	5%	3%	7%	4%	5%	8%	5%
Photophobia	90%	48%	87%	38%	83%	43%	84%	36%*
Phonophobia	83%	44%	82%	28%*	76%	33%	77%	25%*

*p<0.05 vs. placebo

The authors concluded that Imitrex Nasal Spray provided greater relief of migraine than placebo and was generally well-tolerated in adolescents.

Study 2

Ueberall M and Wenzel D (11) published a randomized, double-blind study, placebo-controlled, crossover study evaluating the efficacy of sumatriptan nasal spray in fourteen children with migraine (age range: 6.4 to 9.8 years).

Methods

Patients aged 10 years or younger with an established diagnosis of migraine with or without aura according to the IHS criteria and at least 2 migraines per month were enrolled in the study. Patients were randomized to two alternative treatment strata, in which they received one nasal spray (20 mg sumatriptan) or 0.9% saline solution. After the first migraine, patients received the alternative substance for the next migraine.

Patients assessed outcomes in diaries. Headache intensity was based on a 4-point scale (severe, moderate, mild, no pain) and noted at baseline and at 30 and 60 minutes, continuing every hour for 4 hours. The presence of photophobia, phonophobia, nausea, and vomiting was noted hourly. The primary efficacy endpoint was the reduction of moderate or severe pain to mild or no pain at 2 hours. Children who fell asleep in less than 2 hours were classified as responders, whereas children who required rescue medication were classified as non-responders. Therapeutic gain (TG) (sumatriptan minus the placebo response) and number needed to treat (NNT, 1/TG) were calculated for significant pain reduction (TG_1) and complete response (TG_2).

Results

Fourteen patients (mean age 8.2 years) with median attack duration of 12 hours participated. Eighty-six percent (86%) experienced headache response 2 hours post-dose after sumatriptan nasal spray 20 mg compared with 43% after placebo (p=0.031, TG_1 0.43; 95% CI 0.34 to 0.53; NNT_1 2.3). Total headache relief was obtained in 9 migraines compared with 2 for placebo (64% vs. 14%, p=0.016; TG_2 0.5; 95% CI 0.39 to 0.61, NNT_2=2). Median time to meaningful relief was 30 minutes. Rescue medication was used by 43% of patients after placebo compared with 0% of patients after sumatriptan. Migraine associated symptoms were significantly reduced by sumatriptan. The only adverse event was disturbance of taste both after placebo and sumatriptan (n=2 vs. n=3, respectively). Thirteen of the children preferred sumatriptan (p=0.002; TG, 0.86; 95% CI, 0.81 to 0.92; NNT, 1.16).

The authors suggest sumatriptan nasal spray shows promising results and has an acceptable tolerability profile in children with migraine. Application was simple and easily performed, even by younger children.

IMITREX TABLETS

Placebo-controlled clinical trials evaluating oral sumatriptan (25 to 100 mg) in pediatric patients aged 12 to 17 years have enrolled a total of 701 adolescent migraineurs (2,22,23,24,25) Patients in these studies were diagnosed with a 3 to 6 month history of migraine with or without aura according to the IHS criteria and suffered from 1 to 8 attacks per month. Dosing in two studies was based on weight and is outlined in Table 4.

The primary efficacy endpoint in these studies was headache relief at 2 hours post-dose. Headache relief was defined as reduction of pain intensity from moderate-severe to mild or no pain. These studies did not establish the efficacy at 2 hours of oral sumatriptan compared to placebo in the treatment of migraine in adolescents. Results are outlined in Table 5.

In attempting to explain the lack of significant efficacy of sumatriptan in these patients, the authors of these studies have suggested that the patients may not have been true migraineurs (since only a three-month history was required in some studies). The use of a new combined headache and disability score may not have been as sensitive as the conventional headache severity scale, and the unexpectedly high rate of placebo response should also be considered.

Table 4: Dosing of Imitrex Tablets in Adolescents (9,24,25)

Patient Weight (kg)	Dose of Imitrex
30 to 50 kg	50 mg
>50 kg	100 mg

Table 5: Efficacy of Imitrex Tablets at 2 and 4 hours in Adolescent Migraineurs

Parameter	Placebo	Imitrex 25 mg	Imitrex 50 mg	Imitrex 100 mg
Study 1 (8,23)†	N=76	N=74	N=70	N=78
Headache Relief at 2 hours	42%	49%	50%	51%
Headache Relief at 4 hours	53%	73%*	73%*	74%*
Study 2 (9,24)	N=30		N=28	N=34
Headache Relief at 2 hours‡	25%	NA	35%	25%
Headache Relief at 4 hours‡	32%	NA	68%*	48%
Study 3 (9,25)	N=36		N=35	N=31
Headache Relief at 2 hours‡	42%	NA	30%	50%
Headache Relief at 4 hours‡	57%	NA	39%	75%
Study 4† (22)	N=41	N=73	N=80	N=79
Headache Relief at 2 hours	59%	50%	55%	50%
Headache Relief at 4 hours	56%	58%	64%	66%

* $p<0.05$ vs. placebo † Data from Attack 1 only ‡ A new 4-point combined headache/disability scale was used (0=no headache, 1=headache, but I can carry on as usual, 2=headache, but I can do easy activities, and 3=headache, but I can't do anything). Relief was defined as reduction of grade 2 or 3 to 0 or 1.

Adverse events observed in these clinical trials were similar in nature to those reported in clinical trials in adults. The frequency of all adverse events in these patients appeared to be both dose- and age-dependent, with younger patients reporting events more commonly than older adolescents.

Study 5

Hamalainen et al (10) published a randomized, double-blind, placebo controlled, two-period crossover trial in 23 children aged 8.3 to 16.4 years with a history of migraine for 1-9 years.

Methods

The primary endpoint for clinical efficacy was a $\geq$ 50% decrease in pain intensity on a 100 mm visual analog scale at two hours. Other efficacy endpoints included patient preference, pain intensity difference (PID), sum of pain intensity difference (SPID) and the use of escape analgesia. Based on a body surface area of $\geq 1.5 m^2$ or $< 1.5 m^2$ two and 21 children received sumatriptan 100 mg and 50 mg respectively.

Results

The primary endpoint ($\geq$50% decrease in pain intensity) was reached by 30% and 22% of patients treated with sumatriptan or placebo, respectively. The headache disappeared completely in two hours in 22% and 9% of patients treated with sumatriptan or placebo respectively. Thirteen children preferred sumatriptan while two preferred placebo (p=0.004). The maximum differences in SPIDs were not statistically different at any time points up to four hours. The use of escape analgesia was similar in both groups.

The lack of significant sumatriptan effect may be secondary to the high placebo response rate. A high placebo response rate is not unexpected in the adolescent population and similar results have been observed with other CNS drugs in this population.

IMITREX INJECTION

Two anecdotal reports and two open, prospective studies describing treatment of pediatric patients with Imitrex Injection have appeared in print (4,5,6,7).

Anecdotal Reports

The first of two reports published as abstracts described treatment of migraine with Imitrex Injection in seven children 9 to 16 years of age (4). All seven patients received Imitrex Injection 6 mg SC; within 20-60 minutes all experienced relief of headache. The only reported adverse events were pain at the injection site and feeling "groggy".

A second abstract described administration of Imitrex Injection SC to 17 patients 7 to 18 years of age whose diagnoses included migraine, atypical, complicated, or intractable migraine, and headache (type and diagnostic criteria not specified) (5). Fifteen of the 17 were receiving prophylactic therapy (amitriptyline, cyproheptadine, nonsteroidal anti-inflammatory agents or ergot derivatives). Patients with moderate to severe headache received either 3 mg or 6 mg of Imitrex SC. Vital signs, including blood pressure, were measured prior to the injection and every 15 minutes for 45 minutes thereafter. To assess therapeutic response, patients were asked to rank their headache intensity, before Imitrex vs. 45 minutes after treatment, on a visual analog scale of 1 to 10. Forty-five minutes after injection with Imitrex, 12 of the 17 (71%) reported a decrease in headache ranking by one-half or more. Two patients experienced no relief, i.e. no change in the degree of initial pain, and for the remaining three, pain intensity increased following Imitrex. Reported adverse events were mild and transient, and included flushing, nausea and/or vomiting, and one report each of throat tightness, dizziness, pallor, and diaphoresis.

Open-Label Studies

We are aware of reports of two open-label, prospective studies in which Imitrex was administered to treat acute migraine attacks in patients less than 18 years of age (6, 7). The response to Imitrex was high in both studies, (relief rates of 70% to 72% within one hour). However, the dose of Imitrex differed between the two studies by approximately two-fold, and each study employed different criteria to define efficacy.

In one open-label, prospective study, SC Imitrex was administered to ten female and seven male patients 6 to 16 years of age who met IHS criteria for acute migraine (two patients with aura and 15 without) (6). History of migraine symptoms ranged from one to 12 years (mean of 3.7 years), and 12 of the 17 patients were receiving prophylactic therapy (amitriptyline, propranolol, valproate, or verapamil). Only children whose previous four migraine attacks lasted a minimum of six hours were considered for study treatment, and children with known cardiac disease or current treatment with an ergotamine product were excluded from the study.

Fifteen children whose weights ranged from 30 to 60 kg received a total of 23 doses of Imitrex 6 mg SC; two others (weighing 22 kg and 30 kg respectively) were given one dose each of 3 mg SC. All patients received their initial injections in the presence of a physician, and headache severity (on a subjective scale of 0 to 10) as well as side effects were evaluated at 10-minute intervals for two hours following injection of Imitrex.

Efficacy, defined as absence of headache within two hours of treatment with Imitrex, was demonstrated in 13 of the 17 children (64%). Three mg was an effective dose for the two smaller children, but one of the two was not pain-free until two hours post-injection. Of the 11 children who responded to Imitrex 6 mg SC, six were headache free within one hour, while five other patients required two hours. Responders reported no recurrences with one exception. A 13-year-old boy who had failed in the past to respond to intravenous dihydroergotamine (DHE) was successfully treated with Imitrex, with mild recurrence in 24 hours. Two positive responders subsequently treated a second attack successfully with Imitrex and three others were effectively treated with Imitrex for a total of three separate migraines. The 13 patients who obtained headache relief also reported improvement of phonosensitivity/ photosensitivity and nausea within one hour. The four nonresponders were all girls with mixed headache pattern (chronic daily headache with intermittent acute migraine) who had no improvement of acute migraine attack in response to Imitrex 6 mg; one of these received Imitrex on a second occasion, again with no response.

Side effects were typically mild and of 15 minutes' duration or less. Fifteen patients reported upper chest or neck sensations ("pressure" or "tingling"), two complained of "burning" in the jaw, and one reported a heavy feeling in the head. The author characterized injection site reactions as "very minimal" (6).

In a second, open-label, prospective study, the dose of sumatriptan administered by injection to 50 consecutive children with acute migraine was 0.06 mg/kg SC (7). Twenty-eight females and 22 males, from six to 18 years of age, received Imitrex SC when they presented to a pediatric neurology office with acute migraine (7). Overall efficacy (reduction of headache pain from severe or moderate to mild or none) occurred in 72% of patients by one hour and in 80% within two hours of subcutaneous injection of sumatriptan. Adverse events, reported by 80% of patients, were generally mild and transient, although one patient exhibited a confusional state of two hours duration. Six percent of patients who responded to Imitrex experienced recurrence; the time to recurrence of pain is not noted. The author noted that in this group of pediatric patients, a higher percentage of males responded to Imitrex Injection than females. A statistical analysis of gender-based response was not reported.

CONCLUSION

As noted in the Product Information, the safety and effectiveness of Imitrex® (sumatriptan succinate/sumatriptan), administered either as a subcutaneous (SC) injection, as an oral tablet, or as an intranasal spray has not been established in children (1,2,3). The use of Imitrex in patients less than 18 years of age is not recommended.

One large double-blind, randomized, placebo-controlled trial demonstrated Imitrex Nasal Spray was superior to placebo in relieving migraine and was generally well-tolerated in adolescents and one small study suggested similar results with an acceptable tolerability profile in children.

Studies evaluating the use of Imitrex Tablets in children 6-18 years old have not shown consistent superiority over placebo. The shorter duration of migraine in adolescents and high placebo response rate may explain the inconsistent response seen in this age group.

Two anecdotal reports and two open, prospective studies describe treatment of pediatric patients with Imitrex Injection.

The incidence and pattern of adverse events in children appear to be similar to that observed with adults. Postmarketing experience includes a limited number of reports that describe pediatric patients who have experienced adverse events, some clinically serious, after use of subcutaneous sumatriptan and/or oral sumatriptan. These reports include events similar in nature to those reported rarely in adults (1,2,3).

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Enclosures: Product Information for Imitrex® Injection. Glaxo Wellcome Inc.
Product Information for Imitrex® Tablets. Glaxo Wellcome Inc.
Product Information for Imitrex® Nasal Spray. Glaxo Wellcome Inc.

CSM 27 April 2005

CSM PAEDIATRIC WORKING GROUP

Product: Imigran **MA numbers:** PL 10949/0113, 0260, 0261, 0231, 0222, 0013, 0014 **MAH:** GlaxoSmithKline	
Active constituent: sumatriptan	**Previous Assessments:** 2000 CSM 9 April 2003
Therapeutic classification: Selective $5HT_1$ receptor agonist	**Legal status:** POM

Reason for Committee consideration: Review of paediatric data.

INDEX PAGE

1 Executive Summary

Sumatriptan is a selective $5HT_1$ receptor agonist indicated for the acute treatment of migraine attacks with or without aura.

Sumatriptan nasal spray is authorised in adolescents (12 -17 years of age) for the acute treatment of migraine attacks with or without aura on the recommendation of a specialist or physician who has significant experience in treating migraine, taking into account local guidance.

There are data from one clinical trial that may be considered to demonstrate the efficacy of sumatriptan nasal spray in 7-12 year old patients with migraine. The data from this trial have been previously assessed as part of the Mutual Recognition Procedure variation that resulted in an extension of the indication to include adolescents aged 12-17 years. An adequate assessment of the efficacy and safety findings of this study has not been possible at this occasion due to the absence of a study report.

These data are not considered sufficient to justify an extension of the indication to 7 - 12 year olds because the robustness of the efficacy findings is unclear and there are significant safety concerns in under 18s identified from clinical trials and spontaneous adverse event reports.

Clinical trial data of oral sumatriptan in adolescents are available, but do not support an indication in this patient population. Sumatriptan injection has not been studied in patients under 18 years of age.

The safety profile of sumatriptan is similar in under 18s and adults. There is a continuing safety concern because of reports of stroke and myocardial infarction in adolescents exposed to sumatriptan.

Based on the information provided by the company, there is no evidence to suggest that there are adequate efficacy and safety data to support a favourable risk/benefit evaluation for the use of sumatriptan in paediatric patients younger than 12 years of age.

2 Introduction

The forthcoming EU legislation on medicines for paediatric use will not be finalised before 2006. In the mean time the MHRA has identified a number of actions to enable progress in this area through the current regulatory framework. One of these actions is to formally request completed paediatric study data from companies, where this is known to exist.

In this context, the MHRA contacted companies whose products appear on the US Food and Drug Administration (FDA) Paediatric exclusivity granted list[1]. This is a list of active substances (with relevant sponsors) for which the FDA has granted data exclusivity in return for the submission of paediatric studies carried out in compliance with an FDA written request.

The MHRA only contacted the companies that have not already submitted the data to the UK (or to the European Medicines Agency [EMeA] in the case of a centralised marketing authorisation).

The MHRA contacted GlaxoSmithKline (GSK) on 28 April 2004 requesting the submission of all completed paediatric trial data on the Imigran (sumatriptan) product range as well as a cumulative review of safety.

[1] http://www.fda.gov./cder/pediatric/exgrant.htm

3 Product profile and licensing history

Sumatriptan is a selective 5HTl receptor agonist. Imigran is available in a number of different formulations (Imigran Tablets 50mg and 100mg, Imigran Radis Tablets 50mg and 100mg, Imigran Injection for subcutaneous administration, and Imigran Nasal Spray 10mg and 20mg). All formulations have a prescription only medicine (POM) classification. The solution for subcutaneous injection was first authorised in the UK 1991, followed by the tablet formulation in 1994, the nasal spray in 1996, and the Radis tablet in 2004.

The nasal spray has been authorised elsewhere in the EU through the Mutual Recognition Procedure, with the Netherlands as Reference Member State (RMS). The UK is not involved in this procedure.

All sumatriptan formulations are indicated for the acute treatment of migraine attacks with or without aura in adults. In addition, the 10mg nasal spray is also authorised for use in adolescents as follows:

Adolescents (12-17 years of age).

Use of sumatriptan in adolescents should be on the recommendation of a specialist or physician who has significant experience in treating migraine, taking into account local guidance.

Children (under 12 years of age).
The safety and effectiveness of Imigran Nasal Spray in children has not yet been established.

The recommended dose for adolescents is 10mg for administration into one nostril, i.e. half the dose recommended for adults.

The 20mg nasal spray is only licensed for use in adults.

4 Sumatriptan and FDA paediatric exclusivity

The data submitted to the FDA resulted in a *Not Approvable* action. The FDA concluded that '*the efficacy of Imitrex Nasal Spray has not been demonstrated in adolescents. The adverse event experience essentially mirrored that in the adult data (including rare nasal mucosal changes). Serious but rare adverse events (labeled in adults) have been reported in adolescents in the post-marketing setting (stroke, myocardial infarction, death in overdose, confusion, gastrointestinal bleeding, and visual loss).'*

The FDA has published the assessment report on the internet[2].

5 Marketing Authorisation Holder (MAH) response to MHRA letter

On 28 July 2004, GSK submitted the following:

1. Summary of Clinical Efficacy, including a pooled efficacy analysis from studies SUM30045 and SUMA3005.
2. Summary of Clinical Safety, containing a review of individual case histories for sumatriptan succinate in children less than 18 years received up to 30 April 2004.
3. Study report SUM30045
4. Literature References

[2] http://www.fda.gov/cder/foi/esum/2004/20626se5-004_imitrex_pharm_biopharm_bpca.pdf.

6 Assessment of MAH response

6.1 Clinical Efficacy

6.1.1 Sumatriptan Injection

No paediatric studies have been conducted using the sumatriptan injection.

6.1.2 Sumatriptan Tablets

Eight trials assessed the safety and efficacy of oral sumatriptan in adolescents. The data from these trials have been previously assessed as part of the Mutual Recognition Procedure variation that resulted in an extension of the indication to include adolescents (12-17 years). The study reports were not resubmitted for this assessment. The MA holder states that '*due to high placebo-response rates, no conclusions in regard to efficacy were made from these studies, but the data provide support for the safety and tolerability of sumatriptan in this population*'.

6.1.3 Sumatriptan Nasal Spray

6.1.3.1 Adolescents

Data on the nasal spray are available from six studies (see table 1). Five of these studies were considered as part of a previous variation application that resulted in the grant of a Marketing Authorisation variation for the 12-17 year old population in 2003. These data were not resubmitted and are not considered as part of this assessment.

New data are available from study 30045. In addition, the MAH has supplied a pooled statistical analysis of studies SUMA3005 and SUMA30045.

Table 1: Sumatriptan studies

Protocol	Age range	Duration of treatment	No. migraine attacks treated	Patients received (mg)*				Study population	
				5	10	20	PLC	ITT	Safety
SUMA3005	12–17 yrs	SA, R, DB, PC, PA	510	128	133	118	131	507	510
SUM40019†	8–17 yrs	SA, R, DB, PC, CO	177	—	29	61	87	94	94
SUM30009‡	7–12 yrs	SA, R, DB, PC, CO	117	—	59	—	58	60	60
SUMA3006	12–17 yrs	Up to 12 mo, O	3,272	7	433	197	—	425	437
SUM40276	12–17 yrs	Up to 12 mo, O	4,718	10	—	484	—	452	484
SUM30045#	12–17 yrs	SA, R, DB, PC, PA		255	—	238	245	731	738

- New data.
*Patient numbers according to the safety population; †83 patients completed cross-over; ‡57 patients completed cross-over. The 20mg dose was not included in this study as patients were aged 7–12 years.
SA=single attack, R=randomised, DB=double blind, PC=placebo-controlled, PA=parallel group, CO=cross-over.

Study 30045

Methods

This was a double-blind, placebo-controlled, randomized, parallel-group, single-attack, outpatient study in adolescents (12-17 years of age) with at least a 6-month history of moderate or severe migraine, with or without aura, and at least one, but not more than eight migraine attacks per month in each of the two months preceding enrolment in the study.

Treatment groups included placebo and sumatriptan nasal spray (5mg and 20mg). Subjects were instructed to administer a single dose of investigational product into one nostril. A second dose of investigational product or other acute migraine medications could be taken 2-24 hours later, if migraine pain recurred.

Subjects were required to treat headache pain that became moderate to severe within 30 minutes. A diary was used to record headache intensity and associated symptoms (phonophobia, photophobia, nausea, vomiting) at baseline and at prescribed time points following treatment (including use of any rescue medication).

The primary efficacy endpoints were:

1. the headache relief rates at 1 hour post-dose (sumatriptan 20mg vs. placebo) and
2. sustained relief rates 1 to 24 hours post-dose (sumatriptan 20mg versus placebo)

Headache relief was defined as a decrease in migraine intensity from severe or moderate to mild or no pain without the use of a second dose of study treatment or other headache medication. Sustained headache relief was defined as headache relief without the use of a second dose of study treatment or other headache medication and without a return of severe or moderate headache pain for 24 hours post-dose.

Treatment comparisons were made using the Cochran-Mantel-Haenszel method.

Results (see also tables 2, 3 and 4 below)

A total of 888 subjects were randomized. 738 were treated with investigational product (sumatriptan 5mg n=255, sumatriptan 20mg n=238, placebo n=245) and 731 were evaluable for efficacy and included in the ITT population.

The study failed to reach either of its primary endpoints: The proportion of subjects who achieved headache relief at 1 hour post-dose was 61% in the sumatriptan 20mg group and 52% in the placebo group (p=0.087). The proportion of subjects who achieved ***sustained relief*** was 41% in the sumatriptan 20mg group vs. 32% in the placebo group (p=0.061).

However, at the 20mg dose statistical significance was achieved for headache relief at both at 30min (p=0.046) and 120 min (p=0.025).

No statistically significant difference was observed between the placebo and sumatriptan 5mg groups at any time point.

Assessor's comment

The dose licensed for use in adolescents is 10mg. Study SUMA30045 assessed a dose of 20mg.

The primary efficacy endpoint was the proportion of patients achieving headache response at 1 hour after dosing. Typically, these parameters are assessed at 2 hours, but in the pivotal study SUMA3005, post hoc analyses suggested that adolescents would respond better at 1 hour.

The primary endpoint in pivotal study SUMA3005 was headache relief at 120 minutes. This study had also failed to meet its primary endpoint.

Analysis of pooled data from studies SUMA3005 and SUMA30045

Study SUMA3005 and SUMA30045 were similar in design and study population. Both studies were double-blind, placebo-controlled, randomized, parallel group, single-attack, outpatient studies in adolescents (12-17 years of age). Treatment groups were placebo and sumatriptan nasal spray 5mg, 10mg, and 20mg for SUMA3005, and placebo and sumatriptan nasal spray 5mg and 20mg for SUM30045.

The primary efficacy endpoint for the SUMA3005 study was Headache Relief at 120 minutes post-dose in the 20mg group compared to placebo; in SUM30045 it was Headache Relief at 60 minutes post-dose and Sustained Headache Relief between 1 and 24 hours post-dose.

The following tables provide an overview of the outcome of the individual studies and the pooled analysis. Primary efficacy outcomes are shaded.

Table 2: Headache relief in studies SUMA3005 and SUM30045 (ITT)

	Placebo		**Sumatriptan Dose Group**								
			5 mg			**10 mg**			**20 mg**		
StudyTimepoint	**N/Total (%)**		**N/Total (%)**		**p value**	**N/Total (%)**		**p value**	**N/Total (%)**		**p value**
SUMA3005											
30 minutes	33/130	(25)	32/127	(25)	0.930	44/133	(33)	0.095	39/117	(33)	0.172
60 minutes	53/130	(41)	60/127	(47)	0.346	74/133	(56)	0.011	66/117	(56)	0.026
120 minutes	**70/130**	**(54)**	**84/127**	**(66)**	**0.038**	**85/133**	**(64)**	**0.062**	**74/117**	**(63)**	**0.100**
SUM30045											
30 minutes	79/242	(33)	85/247	(34)	0.610	NA		NA	99/236	(42)	0.046
60 minutes	**127/242**	**(52)**	**132/247**	**(53)**	**0.719**	**NA**		**NA**	**143/236**	**(61)**	**0.087**
120 minutes	141/242	(58)	155/247	(63)	0.278	NA		NA	161/236	(68)	0.025
Pooled											
30 minutes	112/372	(30)	117/374	(31)	0.703	NA		NA	138/353	(39)	0.016
60 minutes	180/372	(48)	192/374	(51)	0.414	NA		NA	209/353	(59)	0.007
120 minutes	211/372	(57)	239/374	(64)	0.037	NA		NA	235/353	(67)	0.005

Table 3: Sustained relief[1] in studies SUMA3005 and SUM30045 (ITT)

			Sumatriptan Dose Group								
	Placebo		**5mg**			**10mg**			**20mg**		
Study	**N/Total (%)**		**N/Total (%)**		**p value**	**N/Total (%)**		**p value**	**N/Total (%)**		**p value**
SUMA3005	35/130	(27)	47/127	(37)	0.093	55/133	(41)	0.007	49/117	(42)	0.017
SUM30045	**78/242**	**(32)**	**92/247**	**(37)**	**0.173**	**NA**		**NA**	**96/236**	**(41)**	**0.061**
Pooled	113/372	(30)	139/374	(37)	0.041	NA		NA	145/353	(41)	0.003

[1]Sustained Headache Relief between 1 and 24 hours was a co-primary endpoint for study SUM30045, but was not prospectively designated as an endpoint for SUMA3005.

In addition to the above parameters, the pooled analysis includes several post-hoc efficacy endpoints, such as *percent of patients pain-free*. The latter parameter is recommended for use as primary endpoint in the *Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment if Migraine (CPMP/EWP/788/01/Final).* The results are summarised in the table below.

Table 4: Percent of patients pain-free in studies SUMA3005 and SUM30045 (ITT)

			Sumatriptan Dose Group								
	Placebo		5mg			10mg			20mg		
StudyTimepoint	N/Total (%)		N/Total (%)		p value	N/Total (%)		p value	N/Total (%)		p value
SUMA3005											
30 minutes	3/130	(2)	3/127	(2)	0.951	4/133	(3)	0.660	5/117	(4)	0.418
60 minutes	12/130	(9)	8/127	(6)	0.507	17/133	(13)	0.281	16/117	(14)	0.240
120 minutes	32/130	(25)	30/127	(24)	0.880	43/133	(32)	0.086	42/117	(36)	0.081
SUM30045											
30 minutes	15/244	(6)	15/250	(6)	0.914	NA		NA	10/237	(4)	0.440
60 minutes	40/244	(16)	49/250	(20)	0.290	NA		NA	55/237	(23)	0.063
120 minutes	73/244	(30)	90/250	(36)	0.116	NA		NA	105/237	(44)	<0.001
Pooled											
30 minutes	18/374	(5)	18/377	(5)	0.965	NA		NA	15/354	(4)	0.691
60 minutes	52/374	(14)	57/377	(15)	0.509	NA		NA	71/354	(20)	0.034
120 minutes	105/374	(28)	120/377	(32)	0.211	NA		NA	147/354	(42)	<0.001

Conclusion on efficacy in adolescents

Both study SUMA3005 and SUM30045 failed to meet their primary endpoints. Statistically significant differences were shown for headache relief at 60 minutes but not at 120 minutes (primary endpoint) in SUMA3005, and at 120 minutes but not at 60 minutes (primary endpoint) in SUM30045. It is noted that the effect size was small in both studies, with a high placebo-response rate and only an additional 10-15% of patients responding to sumatriptan as compared to placebo.

Sumatriptan nasal spray, at a recommended dose of 10mg, has already been licensed for use in adolescents via the mutual recognition procedure. The results of study SUM30045 and the post-hoc pooled analysis, both looking at a 20mg sumatriptan dose, do not provide any robust evidence of efficacy of the 20mg dose.

6.1.3.2 Children aged 7-12 years

Study SUM 30009

This was a single-centre, placebo-controlled, cross-over study conducted in 60 subjects aged 7-12 years. Subjects had at least a six-month history of migraines and inadequate response to the commonly used anti-migraine drugs. Migraines were treated with 10mg sumatriptan nasal spray or placebo nasal spray. 117 migraine attacks were treated.

The primary efficacy endpoint was headache relief at 120 min. Headache relief was defined as at least a 2-point reduction in headache severity from a baseline grade of 2 or 3 on a 4 point scale (where 3=severe, 2=moderate, 1=mild and 0=none).

This was achieved in 24/58 (41%) patients on placebo versus 38/59 (64%) patients on 10mg sumatriptan (p 0.022).

Assessor's comment
The data from this trial have been previously assessed as part of the Mutual Recognition Procedure variation that resulted in an extension of the indication to include adolescents aged 12-17 years but not children aged 7 - 12 years. An adequate reassessment of the efficacy and safety findings of this study has not been possible as part of this present assessment due to the absence of a study report.

Study SUM40019

This study was a three-centre, placebo-controlled, cross-over study conducted in Finland. 94 subjects between the ages of 8-17 years treated migraines with 10mg or 20mg sumatriptan nasal spray (based on body weight) or placebo nasal spray. 177 migraine attacks were treated. 79 of the subjects enrolled were aged 8-11 years.

The primary efficacy endpoint was headache relief at 120 min, combined for the 10mg and 20mg groups. Headache relief was defined as at least a 2 grade reduction in headache severity on a five-grade pictorial scale of facial expressions (where grade 5 is the most severe and grade 1 is the least severe). This was achieved in 38 % patients on placebo versus 67% patients on 10mg and 20mg sumatriptan (p <0.001).

Assessor's comment
The data from this trial have been previously assessed as part of the Mutual Recognition Procedure variation that resulted in an extension of the indication to include adolescents aged 12-17 years, but not children aged 7-12 years. An adequate reassessment of the efficacy and safety findings of this study has not been possible as part of this present assessment due to the absence of a study report.

Published data:

Hershey et al. Effectiveness of nasal sumatriptan in 5 - 12 year old children. Headache 2001;41:693-697
This is a report of a retrospective study of 5mg and 20mg sumatriptan in 10 children aged 5 – 12 years. 7 of 8 patients with headache became headache-free by 45 minutes. The most common side effect was bad taste.

Ueberall et al. Intranasal sumatriptan for the acute treatment of migraine in children. Neurology 1999;52:1507-1510
This is a report of a randomised double-blind placebo-controlled cross-over study in 14 children (6.4 to 9.8 years) with 20mg sumatriptan. Overall, 12 episodes (86%) improved by at least two grades in their pain intensity (primary endpoint) 2 hours after nasal sumatriptan, and 6 (43%) improved after placebo.

Wolf et al. A retrospective chart review of sumatriptan nasal spray as an acute treatment of migraine in children. Headache 2000;40:438 (abstr).
This is a report of a retrospective study of 5mg, 10mg and 20mg sumatriptan in 30 children aged 5 – 12 years. Total relief was reported by 60% of patients. 57% reported bad taste.

Assessor's comment
The published data contribute little to the assessment of efficacy and safety.

Conclusion on efficacy in children aged 7-12 years

There are data from one clinical trial assessing the efficacy of sumatriptan nasal spray in 7-12 year old patients with migraine. These have been assessed previously. An adequate reassessment of the efficacy and safety findings of this study has not been possible due to the absence of a study report. These data are not considered sufficient to justify an extension of the indication to 7 - 12 year olds because the robustness of the efficacy findings is unclear and there are significant safety concerns in under 18s identified from clinical trials and spontaneous adverse event reports.

6.2 Clinical Safety

6.2.1 Clinical Trial Data

Study SUM30045:

There were no serious adverse events or discontinuations due to an adverse event (AE). A dose dependent effect was observed for the overall incidence of adverse events. Events in the nervous system class were most common and included taste disturbance, dizziness, somnolence, smell disturbance, headache, muscle twitching and fasciculation. None of the subjects on sumatriptan had a cardiovascular event or reported chest symptoms.

6.2.2. Cumulative review of safety

At the data lock-point on 30 April 2004, there were 282 reports for patients aged less than 18 years in the MAH's world-wide safety database (273 spontaneous reports and 9 reports from clinical trials or post-marketing studies).

The spontaneous reports concerning children under 18 years comprise 1.6% of the total spontaneous reports received for sumatriptan. Overall, 51 reports (18%) were serious according to regulatory criteria. The age of the children ranged from 2 years to 17 years (median 15 years). 83% (233 cases) concerned adolescents aged 12 to 17 years.

A review of the data shows that the distribution of adverse events across System Organ Classes is broadly similar in the paediatric and adult populations. Table 5 overleaf provides information on the distribution.

Table 5 Body system distribution for children aged <18 years compared with other reports on the sumatriptan adverse event database

SYSTEM ORGAN CLASS	**No. of reports for patients under 18 years of age (n=282)**	**No. of reports for all other patients (n=17,245)**
Nervous system disorders	77 (27%)	3633 (21%)
General disorders and administration site conditions	63 (22%)	5031 (29%)
Gastrointestinal disorders	26 (9%)	1094 (6%)
Respiratory, thoracic and mediastinal disorders	21 (7%)	883 (5%)
Musculoskeletal and connective tissue disorders	16 (6%)	844 (5%)
Skin and subcutaneous tissue disorders	11 (4%)	857 (5%)
Eye disorders	11 (4%)	371 (2%)
Immune system disorders	10 (4%)	292 (2%)
Psychiatric disorders	10 (4%)	427 (2%)
Cardiac disorders	9 (3%)	1017 (6%)
Vascular disorders	9 (3%)	583 (3%)
Injury, poisoning and procedural complications	6 (2%)	406 (2%)
Investigations	5 (2%)	611 (4%)
Pregnancy, puerperium and perinatal conditions	4 (1%)	447 (3%)
Ear and labyrinth disorders	2 (<1%)	108 (< 1%)
Reproductive system and breast disorders	1 (<1%)	173 (1%)
Surgical and medical procedures	1 (<1%)	23 (<1%)
Social circumstances	0 (0%)	79 (<1%)
Renal and urinary disorders	0 (0%)	76 (<1%)
Infections and infestations	0 (0%)	64 (< 1%)
Blood and lymphatic system disorders	0 (0%)	62 (<1%)
Congenital, familial and genetic disorders	0 (0%)	48 (<1%)
Hepatobiliary disorders	0 (0%)	44 (<1%)
Neoplasms benign, (incl cysts and polyps) malignant and unspecified	0 (0%)	31 (<1%)
Metabolism and nutrition disorders	0 (0%)	22 (<1%)
Endocrine disorders	0 (0%)	19 (<1%)

Deaths:
Four fatal cases involving children less than 18 years have been reported:

- One death of a 16-year old involving an overdose of sumatriptan, pseudoephedrine and zolmitriptan.
- One 15-year-old with hydrocephalus was found dead 8 hours after injection of sumatriptan.
- One 9-year old was reported to have died after intranasal sumatriptan, but no further information is available.
- One 13-year old girl died seven months after receiving oral sumatriptan.

There is insufficient information available to establish causality.

Nervous system disorders:

Serious nervous system disorders included cerebrovascular events (n=5), seizures (n=7) and loss of consciousness (n=5). The following table gives an overview of the reports of cerebrovascular events:

Diagnosis	Age/sex	Formulation	Total daily dose	Time to onset
Cerebellar infarction	17Y/M	Injection	6mg	unknown
Cerebrovascular accident	15Y/M	Nasal spray	unknown	2 days
Cerebrovascular accident	14Y/M	Unknown	unknown	unknown
Cerebrovascular accident	17Y/M	Nasal spray	unknown	unknown
Cerebral haemorrhage	15Y/F	Injection	3mg	unknown

Cardiac disorders

There were two serious reports: coronary arteriospasm in a 15 yrs. male and myocardial infarction in a 14 year old male. In addition, there was one non-serious report of supraventricular tachycardia (13 yrs., male) and two non-serious reports of angina pectoris.

6.2.3 Conclusion on safety

The safety profile of sumatriptan is similar in under 18s and adults. There is a continuing safety concern because of reports of stroke and myocardial infarction in adolescents exposed to sumatriptan. The MA holder should make it clear that adverse events observed in adults have also been observed in adolescents. The company should continue to monitor the safety of sumatriptan in adolescents.

6.3 Product Information

6.3.1 MAH proposals for amendment

The MAH proposes the following amendments to the product information:

Injection	
Present SmPC: 4.2 Posology and method of administration Children (under 18 years of age): The safety and effectiveness of Imigran in children has not yet been established.	**Proposed SmPC** 4.2 Posology and method of administration Children and adolescents (under 18 years of age): Sumatriptan Injection has not been studied in adolescents and children, hence the safety and effectiveness of sumatriptan injection in these patient populations has not been established.
Tablets	
Present SmPC: 4.2 Posology and method of administration Children (under 18 years of age): The safety and effectiveness of Imigran in children has not yet been established.	**Proposed SmPC** 4.2 Posology and method of administration Children (under ~~18 years~~ 12 years of age) ~~The safety and effectiveness of Imigran in children has not yet been established.~~ *Sumatriptan tablets have not been studied in children, hence the safety and effectiveness of sumatriptan tablets in this population has not been established.*

	Adolescents (12 to 17 years of age) *Clinical trials in adolescents (12 to 17 years of age) showed high placebo response rates. The efficacy of sumatriptan tablets in this population has therefore not been demonstrated and its use in this age group is not recommended (see section 5.1 Pharmacodynamic Properties).* *Section 5.1 Pharmacodynamic Properties* *A number of placebo-controlled clinical studies assessed the safety and efficacy of oral sumatriptan in 600 adolescent migraineurs aged 12 - 17 years. These studies failed to demonstrate a statistically significant difference in headache relief at 2 hours between placebo and any sumatriptan dose. This was mainly due to the high placebo response rates observed. The undesirable effects profile of oral sumatriptan in adolescents aged 12 - 17 years was similar to that reported from studies in the adult population.*

6.3.2 Assessment of MAH proposals for amendment

The proposed wording for the Injection is considered acceptable. The wording for the Tablets should be amended along the following lines:

Section 4.2 Posology and method of administration: Children and adolescents: Sumatriptan tablets have not been studied in children under 12 years of age. The available clinical trial data in adolescents (12 to 17 years of age) do not support the use of oral sumatriptan in this age group. The use of sumatriptan tablets in children and adolescents is therefore not recommended.

Section 5.1 Pharmacodynamic Properties: ~~A number~~ *(specify number)* of placebo-controlled clinical studies assessed the safety and efficacy of oral sumatriptan in 600 adolescent migraineurs aged 12 - 17 years. These studies failed to demonstrate a statistically significant difference in headache relief at 2 hours between placebo and any sumatriptan dose. ~~This was mainly due to the high placebo response rates observed.~~ The undesirable effects profile of oral sumatriptan in adolescents aged 12 - 17 years was similar to that reported from studies in the adult population.

The PIL for both formulations currently states that '*there is little experience of IMIGRAN in children under 18 years of age or those over 65 years of age so it is not usually prescribed for these age groups'*. This statement should be amended to accurately reflect the information stated in the SmPC.

7 Overall conclusion

Sumatriptan nasal spray, at a recommended dose of 10mg, has been licensed for use in adolescents via the mutual recognition procedure. Neither the newly reported study SUM30045 nor the post-hoc pooled analysis provide robust evidence of efficacy for a sumatriptan dose of 20mg.

The data from the clinical trial using sumatriptan nasal spray in 7-12 year old patients with migraine have been previously assessed as part of the Mutual Recognition Procedure variation that resulted in an extension of the indication to include adolescents aged 12-17 years. An adequate reassessment of the efficacy and safety findings of this study has not been possible as part of this present assessment due to the absence of a study report. These data are not considered sufficient to justify an extension of the indication to 7 - 12 year olds because the robustness of the efficacy findings is unclear and there are significant safety concerns in under 18s identified from clinical trials and spontaneous adverse event reports.

Clinical trial data on oral sumatriptan in adolescents are available, but do not support an indication in this patient population. Sumatriptan injection has not been studied in patients under 18 years of age.

The safety profile of sumatriptan is similar in under 18s and adults. There is a continuing safety concern because of reports of stroke and myocardial infarction in adolescents exposed to sumatriptan.

Based on the information provided by the company, there is no evidence to suggest that there are adequate efficacy and safety data to support a favourable risk/benefit evaluation for the use of sumatriptan in paediatric patients younger than 12 years of age.

8 Recommendations

1. The company should continue to monitor the safety of sumatriptan in adolescents.
2. The product information should be amended as to accurately reflect the available data in children and adolescents.
3. The assessment report should be published on the MHRA website.

CME

Migraine Headaches, Part 3: Hormonal Factors

Jeff Unger, MD; Roger K. Cady, MD; Kathleen Farmer-Cady, PsyD

Continuing Medical Education

Goal

To discuss the work-up and treatment of patients with menstrual migraine and migraine during pregnancy.

Objectives

1. To approach strategies for managing menstrual migraine in the context of hormonal fluctuations and cyclicity.
2. To explore the possible courses of migraine during pregnancy, as well as the differential diagnosis and safe test options.
3. To present safe behavioral, nondrug, and pharmacologic management recommendations for migraineurs during pregnancy and lactation.

Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Albert Einstein College of Medicine and Quadrant HealthCom Inc. Albert Einstein College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

This activity has been peer reviewed and approved by Brian Cohen, MD, professor of clinical OB/GYN, Albert Einstein College of Medicine. Review date: June 2003. It is designed for OB/GYNs.

The Albert Einstein College of Medicine designates this educational activity for a maximum of 1 category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she spent in the educational activity. Participants who answer 70% or more of the questions correctly will obtain credit.

To earn credit, see the instructions on page 51 and mail your answers according to the instructions on page 52.

Disclosure

The Faculty Disclosure Policy of the College of Medicine requires that faculty participating in a CME activity disclose to the audience any relationship with a pharmaceutical or equipment company that might pose a potential, apparent, or real conflict of interest with regard to their contribution to the activity. This disclosure also applies to any discussion of unlabeled or investigational use of any commercial product or device not yet approved in the United States. Dr Unger reports that he is on the speaker's bureau for AstraZeneca, Eli Lilly and Company, GlaxoSmithKline, Merck & Co, Inc, Pfizer Inc, Pharmacia Corporation, and Takeda Pharmaceuticals; and is on the primary care advisory board for AstraZeneca and Primary Care Network. Dr Cady reports that he is on the speaker's bureau for AstraZeneca, GlaxoSmithKline, Merck & Co, Inc, and Pfizer, Inc; is on the advisory board for Abbott Laboratories, Allergan, AstraZeneca, Atrix Laboratories, Inc, Elan Corporation, plc, GlaxoSmithKline, Merck & Co, Inc, and Pfizer Inc; and has received research grant support from Allergan, Inc, AstraZeneca, GlaxoSmithKline, Merck & Co, Inc, Pfizer Inc, Pozen Inc, and Winston Laboratories, Inc. Dr Kathleen Farmer-Cady reports that she has received research grant support from AstraZeneca, GlaxoSmithKline, Merck & Co, and Pozen Inc. Dr Brian Cohen reports no conflict of interest.

The first article in this three-part series [Migraine headaches, part 1: presentation and diagnosis. The Female Patient. *2003;28(5):32-39.] looked at the various symptom patterns and work-up of migraine. The second article [Migraine headaches, part 2: treatment options.* The Female Patient. *2003;28(6):22-29.] discussed both nondrug and pharmacologic therapies. The conclusion of the series considers the role of female hormones, which probably account for the preponderance of women sufferers, in migraine pathogenesis and treatment.*

Migraine is one of the most common disabling medical conditions in women. Approximately 18% of women experience migraine during their reproductive years. The predominance of migraine in women, as well as the associated social and economic burdens, make headache disorders a critical issue in women's health.

MENSTRUAL MIGRAINE

Pathophysiology

Among migraineurs, 60% report an exacerbation of headaches around the time of menstruation (menstrually associated migraine).[1] Of these, 10% of women have true menstrual migraine (ie, occurring exclusively with menstruation). The drop in estrogen levels that accompanies menstruation may trigger migraine in susceptible women. As estrogen levels fall, serotonin production also declines and its elimination is accelerated. Serotonin stabilizes pain receptors in the brain. At the same time, endogenous opioid activity is reduced and endorphin levels decrease.

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Therapy

The treatment of menstrual migraine involves behavioral strategies, preventive measures, and acute therapy. Behavioral approaches include relaxation training, biofeedback, and avoidance of known environmental, dietary, and other triggers. Life-style interventions should also be strictly observed, including a healthy diet, regular sleep and exercise routines, and smoking cessation.

Preventive treatments should be considered when the migraines are frequent and disabling, or if the patient is unable to avoid headache triggers. In general, monophasic oral contraceptives (OCs) are preferred over triphasic formulations. Patients using OCs may have headaches during the 7 days of placebo, and can be instructed to take the OCs for 21 days and immediately start a new pack without using the placebo. After 3 months of noncycled OC usage, the patient should stop taking the pills for 7 days. This may trigger a series of severe headaches, which can be treated using naratriptan, 1 mg twice a day or 2.5 mg taken at 4 AM daily, for 7 days. An additional dosage of naratriptan may be taken once within a 24-hour period for a breakthrough headache. Frovatriptan may be used in a similar manner to prevent menstrual migraine.

Patients who cannot or do not wish to use OCs can consider a transdermal estrogen patch, -estradiol 0.5 mg, applied 3 days prior to the onset of menstruation and replaced once after 3 days.[2] The patch helps to prevent a critical drop in serum estrogen levels that could trigger a migraine. The estrogen patch will not delay menstruation.

Nonsteroidal anti-inflammatory drugs (NSAIDs) may be used on a short-term, scheduled basis beginning 2 to 3 days before the onset of menstruation and continuing until the end of menses. Magnesium, 250 mg/d at bedtime, used alone or in combination with an NSAID around the time of menses, may also have a preventive effect for menstrual migraine.[3]

Postmenopausal women can generally expect an abatement in migraine headaches. However, patients who opt for hormone replacement therapy should avoid "cycling" the estrogen and progesterone, instead taking both together daily. In addition, use of a pure estrogen (eg, estrace, estradiol, estradiol patch) is preferable to using conjugated equine estrogens, which can trigger migraine in some women. Postmenopausal women who continue to experience migraines should use behavioral, acute, and preventive strategies similar to other migraineurs.

PREGNANCY AND LACTATION

Migraine can occur for the first time during pregnancy. The course of preexisting migraine during pregnancy is variable. The headaches worsen in some patients, especially during the first trimester, but headaches improve during pregnancy in about 65% of migraineurs.[4]

Headaches are most likely to worsen during pregnancy among women who had preexisting migraine with aura, while they may improve among women with preexisting true menstrual migraine. In general, headache frequency, intensity, and duration tend to improve over the course of pregnancy, and migraine may remit completely in some patients. However, patients who report headaches at the end of their first trimester tend to continue experiencing migraine throughout pregnancy and the postpartum period.[5]

Pregnancy-related adverse outcomes (spontaneous abortions or stillbirths) are not increased in migraineurs. However, migraineurs have a greater potential for developing toxemia than nonmigraineurs.

Diagnosis

Most patients who experience headaches during pregnancy have primary disorders, such as migraine and episodic tension-type headache. However, secondary headache disorders (eg, meningitis, idiopathic intracranial hypertension, pseudotumor cerebri, subarachnoid hemorrhage) may develop during pregnancy, necessitating diagnostic neuroimaging or a spinal tap. If neuroimaging is required, the study that provides the most information with the least fetal risk is the best choice.

At the time of conception, the most common effect of radiation (at a threshold of 5 rad or more) is death of the conceptus. Radiation exposure at this level during the first trimester may result in developmental anomalies or intrauterine growth retardation. A radiation dose of 15 rad or more can produce deformities that might warrant pregnancy termination. The standard computed tomography (CT) scan of the head exposes the fetus to no more than 1 mrad.[6] Head CT is relatively safe during pregnancy, and is the preferable study for head trauma and subarachnoid hemorrhage.[7] The potential risk of magnetic resonance imaging (MRI) in pregnancy remains controversial. The MRI magnets induce an electric field that raises the core temperature by less than 1°C. While this rise in body temperature may increase the incidence of neural tube defects, MRI may be necessary to investigate pathology.

Gadolinium crosses the placental barrier and is excreted through the fetal kidneys. Although no ill effects have been demonstrated with gadolinium, MRI and CT contrast studies should be avoided during pregnancy.

Therapy

Treating pregnant migraineurs can be challenging. Because of the risk of fetal injury, medication use should be limited. Fortunately, most migraineurs improve enough by the second trimester that nonpharmacologic measures may be sufficient. Behavioral intervention is critical before and during pregnancy.

Individual headaches should be treated when possible with ice packs, reassurance, and relaxation. Nonpharmacologic treatment significantly improves headache symptoms in 79% of pregnant patients.[7] For moderate to severe headaches, NSAIDs, acetaminophen (alone or with codeine), or narcotics (meperidine suppositories) may be used. Patients who experience severe headaches associated with nausea, vomiting, and dehydration may require inpatient care. Dehydration and electrolyte imbalance may pose a greater risk to the fetus than analgesics.

Patients who experience severe nausea with an acute migraine can be treated with antiemetic injections or suppositories. Chlorpromazine, prochlorperazine, promethazine, and trimethobenzamide are available orally, parenterally, and by suppository, and all can be used safely in pregnancy.

Some women develop new daily persistent headache (NDPH) during pregnancy. These intense headaches occur on a daily basis in association with migraine-associated symptoms. Pregnant patients with NDPH may obtain significant relief from occipital nerve blocks.

Another safe, effective treatment for acute migraine during pregnancy is intravenous (IV) magnesium sulfate, a drug that is also helpful in managing patients with toxemia. Magnesium sulfate, 1 g IV push, can be given over 1 to 2 minutes in patients with severe headache. Patients often report a significant "hot flash" for 30 to 45 seconds during the injection. However, nearly 87% of patients experience complete and rapid headache relief, as well as dissipation of other migraine-associated symptoms.[8]

As migraine is most common in women of childbearing age, it is likely that migraineurs will use acute therapies (eg, triptans) before they know they are pregnant. In the United States, sumatriptan is currently labeled pregnancy category C (not recommended for use during pregnancy unless the benefit justifies the potential risk to the fetus). Recent pregnancy registries suggest that there is no evidence of any specific effect of sumatriptan on pregnancy outcome, although the sample size is insufficient to make definitive conclusions about events that occur at a frequency of less than 1 per 1,000.[9] Patients who inadvertently use sumatriptan during early pregnancy can be reassured, and the pregnancy registered so that further data can be obtained.

The estimated teratogenic and congenital fetal malformation risk in women who inadvertently use sumatriptan during pregnancy has been calculated at 2.7%, compared with a general-population risk of 3.6%. However, current information is insufficient to rule out small increases in the risk of birth defects seen with inadvertent sumatriptan exposure during pregnan-

TABLE. Guidelines for Migraine Prevention During Pregnancy

Drug	Dosing Range	FDA Risk Category*
-Blockers		
Atenolol	25-50 mg/d	D
Nadolol	20-40 mg/d	C
Propranolol	40-320 mg/d	C
Antidepressants		
Amitriptyline	10-125 mg/d	D
Doxepin	10-125 mg/d	C
Fluoxetine	10-80 mg/d	C
Nortriptyline	10-100 mg/d	D
Paroxetine	10-40 mg/d	C
Sertraline	25-100 mg/d	C
Calcium-channel Blockers		
Amlodipine	2.5-10 mg/d	C
Verapamil	240-720 mg/d	C
Anticonvulsants		
Divalproex	500-1,000 mg/d	D
Gabapentin	300-2,400 mg/d	C
Topiramate	100-200 mg/d	C

FDA = Food and Drug Administration

*FDA risk categories: A = Controlled human studies show no risk. B = No evidence of risk in humans, but there are no controlled human studies. C = Risk to humans has not been disproved. D = There is strong evidence of risk to the human fetus, but use may be justified in certain situations where the benefit outweighs the potential risk.

cy. For this reason, caution should be exercised in making a positive recommendation for the use of sumatriptan during pregnancy.[10] The risk may or may not be similar for other triptans with a different chemical structure.

An increase in the frequency, intensity, or duration of migraine, as well as the presence of debilitating migraine-associated symptoms, may require the use of preventive medications during pregnancy. Migraine prophylactic drugs should be used only as a last resort, and only after their risks and benefits have been fully disclosed to the patient. Preventive medications should be considered when a patient experiences three or four disabling headaches per month, has headaches that result in dehydration and possible fetal distress, or has headaches that do not improve with the use of acute therapy. The Table lists drugs that may be useful in migraine prevention.

Headache patients who are breast-feeding may safely use acetaminophen, NSAIDs, or narcotics. Triptans should be used with caution; those with a short half-life are preferred, and mothers should pump their breasts to empty them during the 4 to 6 hours after triptan use before resumption of breast-feeding. Stored breast milk may be used in the interim. Ergotamines (Cafergot, dihydroergotamine) are contraindicated during lactation. In general, patients should be cautioned against using acute migraine drugs during lactation unless the benefits significantly outweigh the risks.

CONCLUSION

Physicians, like coaches, can help the migraineur live a more pain-free and disability-free existence, but the patient must take the primary responsibility. Patients must comply with the recommended behavioral modifications. They should receive headache information from a reliable source, and discuss advice from well-meaning relatives, friends, nutrition advocates, and talk-show guests with the physician. A trusting relationship between physician and patient should result in a significant improvement in the patient's headaches. Patients should be given educational materials and keep a headache diary to help them adjust management strategies with their physicians.

The goals for patients and physicians may be different. Patients generally want to be pain-free, which is not always attainable. Physicians want patients to decrease migraine frequency, intensity, and duration by at least 50% while demonstrating a significant improvement in their quality of life. Today, physicians can treat migraines successfully in more than 90% of patients within the primary care setting. Given the availability of new and improved migraine medications, there is no reason for patients to continue to suffer.

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Additional Resources

National Headache Foundation (NHF). 428 W. St. James Place. 2nd Floor. Chicago, IL 60614;1-888-NHF-5552.

American Council for Headache Education (ACHE). 19 Mantua Road. Mt. Royal, NJ 08061; 1-800-255-ACHE. www.achenet.org.

Primarycarenet.org

Headachecare.com

MEDICAID TARGET LIST FOR B4EN15 (TOP 50 PRESCRIBERS)

Prescriber	Zip	Total Details	Imitrex (Tablet) Medicaid Market Share (%)
LAURENCE S LOPEZ	80903	8	3.5%
GORDON R GOLDEN	80918	3	0.0%
JEAN E TEASLEY	80907	38	60.2%
CHARLES L JOHNSON	80909	3	51.3%
MARK C WARWICK	80907		3.4%
SUSAN E DATTILO	80907	4	16.7%
KATHARINE J LEPPAR	80909	8	35.0%
MICHAEL A YOESEL	80918	1	74.4%
ANTHONY J CHRISTOI	80907		0.0%
WENDY K DAY	80920	3	0.0%
JACK R ZIMMERMAN	80909		8.0%
JOEL B KLEIN	80863	7	0.0%
JACK L ROOK	80909	4	51.1%
PATRICIA A FODOR	80909		0.0%
JOHN W BAER	80909	2	33.7%
JOHN M MCMAHON	80911	4	19.3%
MUNNI R SELAGAMSI	80903	1	15.0%
GARY V GIERINGER	80909	11	10.4%
JANAKKUMA G JOSHI	80909	2	39.3%
LAURA L FELDMAN	80906	5	46.8%
BRIAN E GRABERT	80907	27	85.3%
AZMI E FARAG	80909	1	0.0%
DANIEL R FELLHAUEI	80918	10	100.0%
KENNETH P FINN	80903	3	0.0%
JAMES D BROOKE	80910	2	28.3%
ORLANDO R DEHERRI	80903		0.0%
DOUGLAS G SWANSO	80910	19	99.6%
KELLY R GREGG	80918	3	8.3%
LAURENCE J ADAMS	80909	3	0.0%
ROBIN L MORGAN	80909	5	100.0%
JAMIESON D KENNED	80904	2	0.0%
ROBERT L ZIMMERM/	80903		53.8%
MARK S FRALEY	80909	2	100.0%
RICHARD J KOURI	80918	4	44.0%
THOMAS O WEBER	80910		72.2%
JOHN M TYLER	80909		72.8%
SHELDON J RAVIN	80903	10	24.6%
JASHIM U AHMED	80909	2	96.2%
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RANDALL G HOFFMAI	80903	2	0.0%
BRUCE H PETERS	80907	3	100.0%

LAMICTAL®
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TABLETS

SELLING RESOURCE

Semester II – 2001

LAMICTAL® (LAMOTRIGINE) TABLETS

COREG® Carvedilol

Wellbutrin SR® (bupropion HCl)

LAMICTAL®
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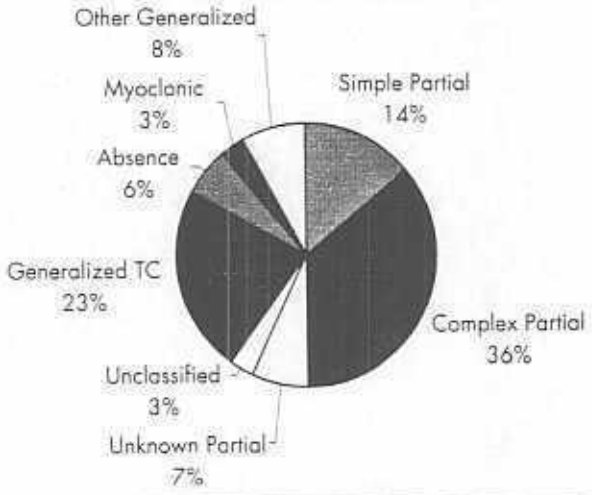
TABLETS

Incidence of Epilepsy Characterized by Seizure Type

Hauser, et al. *Epilepsia.* 1993;34:453-468



Market Growth—Epilepsy

	Rolling QTR Ending 4/01 NRX Volume (000)	Rolling QTR Ending 4/01 NRX % Growth vs. SQLY	Rolling QTR Ending 4/01 TRX Volume (000)	Rolling QTR Ending 4/01 TRX % Growth vs. SQLY
LAMICTAL	88	6%	273	12%
Dilantin	427	-11%	1,423	-9%
Tegretol	325	0%	1,117	0%
Phenobarbital	323	-2%	859	-1%
Neurontin	79	-31%	252	-20%
Depakote	138	-19%	596	-13%
Topamax	96	39%	195	10%
Carbatrol	40	38%	140	46%
Gabitril	13	63%	32	19%
Felbatol	5	-17%	17	-6%
Keppra	31	N/A	77	N/A

Source: Scott-Levin
SQLY - Same Quarter Last Year

AED Total Prescriptions (000)

	TRXs MAT 4/00	TRXs MAT 4/01	% Share	% Change
TOTAL	**39,219**	**44,672**	**100%**	**14%**
Older Agents	**27,438**	**27,511**	**61.6%**	**0%**
Depakote/divalproic sodium	8,885	9,174	20.5%	3%
Dilantin/phenytoin	8,328	8,352	18.7%	0%
Tegretol/XR/carbamazepine	6,552	6,328	14.2%	-3%
Phenobarbital	3,674	3,658	8.2%	0%
Newer Agents	**11,781**	**17,162**	**38.4%**	**46%**
Neurontin/gabapentin	8,273	11,590	25.9%	40%
LAMICTAL/lamotrigine	**1,005**	**1,279**	**2.9%**	**27%**
Topamax/topiramate	756	1,641	3.7%	117%
Carbatrol/carbamazepine	442	699	1.6%	58%
Gabitril/tiagabine	131	132	0.3%	1%
Felbatol/felbamate	73	71	0.2%	-3%
Zonegran/zonisamide	0	65	0.1%	N/A
Trileptal/oxcarbazepine	20	358	0.8%	>999%
Keppra/levetiracetam	1	214	0.5%	>999%
Total Others	1,079	1,110	2.5%	3%

Source: Scott-Levin SPA
NOE: Unfactored Data

- ☐ LAMICTAL is effective as adjunctive therapy for both partial seizures (adults) and the generalized seizures of LGS (adults and children).
- ☐ LAMICTAL is an effective monotherapy agent following conversion from a single enzyme-inducing AED (EIAED) for adults with partial seizures.

Total Prescriptions (000) for Epilepsy

	TRXs MAT 4/00	TRXs MAT 4/01	% Share	% Change
TOTAL	**20,932**	**21,436**	**100%**	**2%**
Older Agents	**17,168**	**16,767**	**78.2%**	**-2%**
Depakote/divalproic sodium	2,742	2,603	12.1%	-5%
Dilantin/phenytoin	6,508	6,058	28.3%	-7%
Tegretol/XR/carbamazepine	4,453	4,577	21.4%	3%
Phenobarbital	3,464	3,529	16.5%	2%
Newer Agents	**3,763**	**4,667**	**21.8%**	**24%**
Neurontin/gabapentin	1,311	1,114	5.2%	-15%
LAMICTAL/lamotrigine	**863**	**1,038**	**4.8%**	**20%**
Topamax/topiramate	550	814	3.8%	48%
Carbatrol/carbamazepine	300	505	2.4%	68%
Gabitril/tiagabine	106	121	0.6%	14%
Felbatol/felbamate	73	71	0.3%	-3%
Zonegran/zonisamide	-	64	0.3%	N/A
Trileptal/oxcarbazepine	13	231	1.1%	>999%
Keppra/levetiracetam	-	208	1.0%	N/A
Total Others	549	504	2.4%	-8%

Source: Scott-Levin SPA
NOE: Unfactored Data

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TABLETS

OPENING

Open Questions
(facilitates information gathering...encourages dialogue/discussion. Best method for uncovering customer needs.)

- ☐ What is your protocol if you can't control seizures? How do you define control?
- ☐ Can you describe some of your patients who are not being effectively managed on their current AED regimen?
- ☐ How "refractory" do patients have to be before you refer them to a tertiary care center?
- ☐ What makes a patient refractory?
- ☐ What is the main concern of patients with less frequent seizures?
- ☐ What factors affect your selection of AED: pharmacokinetics, drug interactions, AE profile, efficacy, cost?
- ☐ How often do you follow your patients? How often do you reassess treatment?
- ☐ How do you define success when treating your active patients with partial seizures?

Closed Questions
(obtains yes/no answers...not productive in gathering information. Directs the conversation.)

- ☐ Are your patient's seizures effectively managed?
- ☐ Doctor, are your epilepsy patients completely satisfied with their AED medication?
- ☐ What percentages of the patients you see are on monotherapy vs. polytherapy?
- ☐ Did you know that 64% of patients in the Roper Poll switched AEDs for improved seizure control?
- ☐ Doctor, LAMICTAL is available in two formulations, tablets and chewable-dispersible tablets. Which formulation do you use most often?

LAMICTAL® (LAMOTRIGINE) TABLETS

IDENTIFY NEEDS/CREATING NEEDS ⟷ PRESENT POSITIONING VALUE
(Features/Benefits)

Need for: Efficacy/Control

Positioning Value

- ☐ Feature: Proven efficacy as adjunctive therapy in Lennox-Gastaut syndrome, a severe and often difficult to treat epilepsy.
- ☐ Benefit: Therefore, doctor, you can have confidence in adding LAMICTAL to help manage those seizures.

- ☐ Feature: LAMICTAL has a conversion to monotherapy indication for adult patients receiving treatment with a single EIAED.
- ☐ Benefit: A monotherapy regimen may help compliance.

- ☐ Feature: In Gilliam conversion to monotherapy trial, 56% of the patients completed the trial. This was more than two times greater than the proportion of patients in the control group.
- ☐ Benefit: What this means is that your patients can feel confident when converting to monotherapy on LAMICTAL.

- ☐ Feature: Proven efficacy as adjunctive therapy for adult patients with partial seizures.
- ☐ Benefit: Confidence with LAMICTAL as the add-on of choice in appropriate patients to help manage those seizures.

Need for: Established AED

Positioning Value

- ☐ Feature: Doctor, LAMICTAL has been used in over 93 countries & 2.8 million patients worldwide.
- ☐ Benefit: Physicians and patients can feel confident when using LAMICTAL—an established AED with proven efficacy.

- ☐ Feature: Doctor, LAMICTAL is an established AED used in the US market for over 6 years.
- ☐ Benefit: Physicians and patients can feel confident when using LAMICTAL—an established AED with proven efficacy.

- ☐ Feature: Doctor, LAMICTAL is an established AED with proven efficacy as (1) adjunctive therapy for both partial seizures (adults), (2) the generalized seizures of Lennox-Gastaut syndrome (adults and children), and when (3) converted to monotehrapy from a singe enzyme-inducing AED in adults with partial seizures.
- ☐ Benefit: Therefore, doctor, you can have confidence in adding LAMICTAL or converting to monotherapy in appropriate patients to help manage those seizures.

LAMICTAL®
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TABLETS

HANDLING RESISTANCE

Newer AEDs vs. Older AEDs

Objection: I don't feel comfortable using a new drug like LAMICTAL for conversion to monotherapy. I would prefer to start with one of the older AEDs.

Solution: LAMICTAL is an established AED with proven efficacy as (1) adjunctive therapy for both partial seizures (adults), (2) the generalized seizures of LGS (adults & children), and when (3) converted to monotherapy from a single EIAED in adults with partial seizures.

Sales Tool: Gilliam Reprint (LMT 533), Motte Reprint (LMT 534)

Objection: How does LAMICTAL compare to the older AEDs, Dilantin and Tegretol?

Solution: There are data available from European studies which suggest comparable efficacy relative to Dilantin and Tegretol in newly diagnosed (monotherapy) patients, which is not an approved use of LAMICTAL.

Resources: Steiner WLF Reprint (LMT 447), Brodie WLF Reprint (LMT 456), Brodie Elderly WLF Reprint (LMT 483), FaxBack Letter #8

Dosing and Titration

Objection: The dosing and titration for LAMICTAL are too complex.

Solution:

- Clarify which patient type and review appropriate dosing guidelines.
- Review charts in PI.
- Dose escalation packs will assist with titration phase.
- Time to titration vs. Long-term benefits of control

Sales Tools: Adult Dosing Card (LMT 518), Dose Escalation Sample Packs, PI

Rash

Objection: I am concerned about rash with LAMICTAL.

Solution:

- Address concerns and contact local NeuroHealth counterpart to coordinate and optimize best long-term response to rash.

- PI states in adult premarketing trials:
  - 10% experienced rash (5% placebo)
  - 3% discontinued trials due to rash in premarketing clinical trials
  - 0.3% (3/1000) experienced serious rash (Serious is defined as hospitalization and discontinuation of treatment.)
- PI states in pediatric premarketing clinical trials:
  - 3.9% discontinued because of rash
  - 1% (1/100) experienced serious rash (requiring hospitalization and discontinuation)
- Evidence suggests risk of rash may be increased by: (1) co-administration of LAMICTAL with Valproic Acid, (2) exceeding recommended initial dose of LAMICTAL, and (3) exceeding the recommended dose escalation for LAMICTAL.

Dose Escalation Packs can help ensure proper titration.

LAMICTAL should ordinarily be discontinued at the first sign of rash unless the rash is clearly not drug related.

Sales Tools: PI, Dose Escalation Packs

Other Resources: If physician asks if any additional data are available, you may refer him/her to FaxBack Letter #1.

Bipolar

Issue: Do you have any efficacy data on LAMICTAL for bipolar depression?

Response: Please see revised LAMICTAL FaxBack Letter.

Tools: Calabrese WLF Reprint (LMT 408), FaxBack Letter #5

Issue: I recently read an article in the *Journal of Clinical Psychiatry* on the use of LAMICTAL in treating rapid cycling bipolar patients. Do you have any additional data on that use?

Response: Please see revised LAMICTAL FaxBack Letter.

Tool: FaxBack Letter #5

LAMICTAL®
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TABLETS

CLOSING

Temperature Check (uncover obstacles–establish intent to prescribe)

- ☐ Doctor, as we discussed, 56% of the patients completed Gilliam's conversion to monotherapy trial. Do you see the advantage of converting your adult patients on single EIAEDs (e.g., carbamazepine and phenytoin) to monotherapy with LAMICTAL?
- ☐ Doctor, knowing that many of your epilepsy patients would prefer monotherapy to polytherapy, do you feel comfortable in converting appropriate patients to monotherapy with LAMICTAL?
- ☐ Doctor, the data I've presented to you illustrates how well LAMICTAL works for your patients. Will you add LAMICTAL for your adult epilepsy patients who are experiencing partial seizures?
- ☐ Doctor, knowing that LAMICTAL demonstrated statistically significant reduction in median seizure counts compared with placebo, do you feel your pediatric patients with generalized seizures of Lennox-Gastaut syndrome would benefit from LAMICTAL?
- ☐ Doctor, based on the fact that unlike Dilantin, LAMICTAL demonstrates linear kinetics, would you agree that this makes LAMICTAL more convenient to dose?

Close the Call (action-oriented–request)

- ☐ Doctor, for those patients who you are treating with multiple medications that may include LAMICTAL, will you convert to monotherapy with LAMICTAL?
- ☐ Based on the information I've provided, will you add LAMICTAL to your adult patients on EIAEDs?
- ☐ Doctor, based on the information we discussed, will you choose LAMICTAL as the first add-on agent in your appropriate patients?
- ☐ Doctor, for your adult patients with partial seizures that are not controlled on their current therapies, will you add LAMICTAL?
- ☐ You have agreed that LAMICTAL offers your patients the efficacy they deserve, coupled with an established safety profile. With this said, will you prescribe LAMICTAL?
- ☐ Doctor, will you prescribe the LAMICTAL chewable dispersible tablets for your patients with the generalized seizures of Lennox-Gastaut syndrome?